

WHAT IS CLAIMED IS:

1. A method for associating a gene G in the genome of a species with a clinical trait T exhibited by one or more organisms in a plurality of organisms of said species, the method comprising:
 - 5 (A) identifying an expression quantitative trait loci (eQTL) for said gene G using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an organism in said plurality of organisms;
 - 10 (B) identifying a clinical quantitative trait loci (cQTL) that is linked to said clinical trait T using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values is a phenotypic value for said clinical trait T in an organism in said plurality of organisms; and
 - 15 (C) determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene G is associated with said clinical trait T.
2. The method of claim 1, wherein said determining step further comprises
20 determining whether the locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species, wherein, when said locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species, the association between said gene G and said clinical trait T is confirmed.
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3. The method of claim 2, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 3cM of each other in the genome of said species.
- 30 4. The method of claim 2, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 1cM of each other in the genome of said species.

5. The method of claim 1, wherein said eQTL and said cQTL are not colocalized unless a test for pleiotropy indicates that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL.

5 6. The method of claim 1, wherein said first QTL analysis and said second QTL analysis each uses a genetic map.

7. The method of claim 6, which further comprises, prior to the first identifying step, a step of constructing said genetic map from a set of genetic markers
10 associated with said plurality of organisms.

8. The method of claim 7, wherein said set of genetic markers comprises single nucleotide polymorphisms (SNPs), microsatellite markers, restriction fragment length polymorphisms, short tandem repeats, DNA methylation markers, sequence length
15 polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

9. The method of claim 7, wherein genotype data is used in said constructing step and wherein said genotype data comprises knowledge of which alleles, for each
20 marker in said set of genetic markers, are present in each organism in said plurality of organisms.

10. The method of claim 7, wherein said plurality of organisms represents a segregating population and pedigree data is used in said constructing step, and wherein
25 said pedigree data shows one or more relationships between organisms in said plurality of organisms.

11. The method of claim 10, wherein said plurality of organisms comprises an F2 population, a F₁ population, a F_{2:3} population, or a Design III population and said one
30 or more relationships between organisms in said plurality of organisms indicates which organisms in said plurality of organisms are members of said F2 population, said F₁ population, said F_{2:3} population, or said Design III population.

12. The method of claim 1, wherein each said expression value is a normalized expression level measurement for said gene G in an organism in said plurality of organisms.

5 13. The method of claim 12, wherein each said expression level measurement is determined by measuring an amount of a cellular constituent that corresponds to said gene G in one or more cells from an organism in said plurality of organisms.

10 14. The method of claim 13, wherein said amount of said cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, an abundance of a protein in said one or more cells of said organism, an abundance of an mRNA expressing said gene, or a degree of protein modification.

15 15. The method of claim 14, wherein said abundance of said RNA is measured by a method comprising contacting a gene transcript array with said RNA from said one or more cells of said organism, or with nucleic acid derived from said RNA, wherein said gene transcript array comprises a positionally addressable surface with attached nucleic acids or nucleic acid mimics, wherein said nucleic acids or nucleic acid mimics are capable of hybridizing with said RNA species, or with nucleic acid derived from said
20 RNA species.

16. The method of claim 12, wherein said normalized expression level measurement is obtained by a normalization technique selected from the group consisting of Z-score of intensity, median intensity, log median intensity, Z-score standard deviation
25 log of intensity, Z-score mean absolute deviation of log intensity, calibration DNA gene set, user normalization gene set, ratio median intensity correction, and intensity background correction.

17. The method of claim 1, wherein said first QTL analysis comprises:
30 (i) testing for linkage between (a) the genotype of said plurality of organisms at a position in the genome of said species and (b) said plurality of expression statistics for gene G;
(ii) advancing the position in said genome by an amount; and
(iii) repeating steps (i) and (ii) until all or a portion of the genome of said species
35 has been tested.

18. The method of claim 17, wherein said amount is less than 100 centiMorgans.
- 5 19. The method of claim 17, wherein said amount is less than 10 centiMorgans.
20. The method of claim 17, wherein said amount is less than 5 centiMorgans.
21. The method of claim 17, wherein said amount is less than 2.5
10 centiMorgans.
22. The method of claim 17, wherein said testing comprises performing linkage analysis or association analysis.
- 15 23. The method of claim 22, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.
24. The method of claim 23, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.
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25. The method of claim 24, wherein said eQTL is represented by a lod score that is greater than 2.0.
26. The method of claim 24, wherein said eQTL is represented by a lod score
25 that is greater than 3.0.
27. The method of claim 24, wherein said eQTL is represented by a lod score that is greater than 4.0.
- 30 28. The method of claim 24, wherein said eQTL is represented by a lod score that is greater than 5.0.
29. The method of claim 1, wherein said second QTL analysis comprises:
(i) testing for linkage between (a) the genotype of said plurality of organisms at a
35 position in the genome of said species and (b) said plurality of phenotypic values;

(ii) advancing the position in said genome by an amount; and
(iii) repeating steps (i) and (ii) until all or a portion of the genome of said species has been tested.

5 30. The method of claim 29, wherein said amount is less than 100 centiMorgans.

 31. The method of claim 29, wherein said amount is less than 10 centiMorgans.

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 32. The method of claim 29, wherein said amount is less than 5 centiMorgans.

 33. The method of claim 29, wherein said amount is less than 2.5 centiMorgans.

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 34. The method of claim 29, wherein said testing comprises performing linkage analysis or association analysis.

 35. The method of claim 34, wherein said linkage analysis or association
20 analysis generates a statistical score for said position in the genome of said species.

 36. The method of claim 35, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

25 37. The method of claim 36, wherein said cQTL is represented by a lod score that is greater than 2.0.

 38. The method of claim 36, wherein said cQTL is represented by a lod score that is greater than 3.0.

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 39. The method of claim 36, wherein said cQTL is represented by a lod score that is greater than 4.0.

 40. The method of claim 36, wherein said cQTL is represented by a lod score
35 that is greater than 5.0.

41. The method of claim 1, wherein said plurality of organisms is human.
42. The method of claim 1, wherein said clinical trait T is a complex trait.
- 5 43. The method of claim 42, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.
44. The method of claim 42, wherein said complex trait is a disease that is
10 contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.
45. The method of claim 42, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.
- 15 46. The method of claim 42, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.
47. The method of claim 42, wherein said complex trait is associated with a
20 high frequency of disease-causing alleles in said species.
48. The method of claim 42, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.
- 25 49. The method of claim 42, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine,
30 nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

50. The method of claim 1, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 40 cM of the physical location of the cQTL in said genome.

5 51. The method of claim 1, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 20 cM of the physical location of the cQTL in said genome.

52. The method of claim 1, wherein said eQTL and said cQTL colocalize to
10 the same locus in the genome of said species when the physical location of the eQTL in said genome is within 10 cM of the physical location of the cQTL in said genome.

53. The method of claim 1, wherein said eQTL and said cQTL colocalize to
15 the same locus in the genome of said species when the physical location of the eQTL in said genome is within 6 cM of the physical location of the cQTL in said genome.

54. A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism
20 for associating a gene G in the genome of a species with a clinical trait T exhibited by one or more organisms in a plurality of organisms of said species, the computer program mechanism comprising:

an expression quantitative trait loci (eQTL) identification module for identifying an expression quantitative trait loci (eQTL) for said gene G using a first quantitative trait
25 loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an organism in said plurality of organisms;

a clinical quantitative trait loci (cQTL) identification module for identifying a
30 clinical quantitative trait loci (cQTL) that is linked to said clinical trait T using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for said clinical trait T in an organism in said plurality of organisms; and

a determination module for determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene G is associated with said clinical trait T.

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55. The computer program product of claim 54, wherein said determining further comprises determining whether the locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species, wherein, when said locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species said gene G is associated with said clinical trait T.

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56. The computer program product of claim 55, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 3cM of each other in the genome of said species.

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57. The computer program product of claim 55, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 1cM of each other in the genome of said species.

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58. The computer program product of claim 54, wherein said eQTL and said cQTL are not considered colocalized unless a test for pleiotropy indicates that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL.

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59. The computer program product of claim 54, wherein said first QTL analysis and said second QTL analysis each uses a genetic map.

60. The computer program product of claim 59, the computer program mechanism further comprising a genetic map construction module for constructing said genetic map from a set of genetic markers associated with said plurality of organisms.

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61. The computer program product of claim 60, wherein said set of genetic markers comprises single nucleotide polymorphisms (SNPs), microsatellite markers, restriction fragment length polymorphisms, short tandem repeats, DNA methylation

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markers, sequence length polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

62. The computer program product of claim 60, wherein genotype data is used
5 by said genetic map construction module and wherein said genotype data comprises knowledge of which alleles, for each marker in said set of genetic markers, are present in each organism in said plurality of organisms.

63. The computer program product of claim 60, wherein said plurality of
10 organisms represents a segregating population and pedigree data is used in said constructing step, and wherein said pedigree data shows one or more relationships between organisms in said plurality of organisms.

64. The computer program product of claim 63, wherein said plurality of
15 organisms comprises an F₂ population, a F₁ population, a F_{2:3} population, or a Design III population and said one or more relationships between organisms in said plurality of organisms indicates which organisms in said plurality of organisms are members of said F₂ population, said F₁ population, said F_{2:3} population, or said Design III population.

65. The computer program product of claim 54, wherein each said expression
20 value is a normalized expression level measurement for said gene G in an organism in said plurality of organisms.

66. The computer program product of claim 65, wherein each said expression
25 level measurement is determined by measuring an amount of a cellular constituent that corresponds to said gene G in one or more cells from an organism in said plurality of organisms.

67. The computer program product of claim 66, wherein said amount of said
30 cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, an abundance of a protein in said one or more cells of said organism, an abundance of an mRNA expressing said gene, or a degree of protein modification.

68. The computer program product of claim 67, wherein said abundance of
35 said RNA is measured by a method comprising contacting a gene transcript array with

said RNA from said one or more cells of said organism, or with nucleic acid derived from said RNA, wherein said gene transcript array comprises a positionally addressable surface with attached nucleic acids or nucleic acid mimics, wherein said nucleic acids or nucleic acid mimics are capable of hybridizing with said RNA species, or with nucleic acid
5 derived from said RNA species.

69. The computer program product of claim 68, wherein said normalized expression level measurement is obtained by a normalization technique selected from the group consisting of Z-score of intensity, median intensity, log median intensity, Z-score
10 standard deviation log of intensity, Z-score mean absolute deviation of log intensity, calibration DNA gene set, user normalization gene set, ratio median intensity correction, and intensity background correction.

70. The computer program product of claim 54, wherein said first QTL
15 analysis comprises:

- (i) testing for linkage between (a) the genotype of said plurality of organisms at a position in the genome of said species and (b) said plurality of expression statistics for gene G;
- (ii) advancing the position in said genome by an amount; and
20 (iii) repeating steps (i) and (ii) until a portion of the genome of said species has been tested.

71. The computer program product of claim 70, wherein said amount is less than 100 centiMorgans.
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72. The computer program product of claim 70, wherein said amount is less than 10 centiMorgans.

73. The computer program product of claim 70, wherein said amount is less than 5 centiMorgans.
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74. The computer program product of claim 70, wherein said amount is less than 2.5 centiMorgans.

75. The computer program product of claim 70, wherein said testing comprises performing linkage analysis or association analysis.

76. The computer program product of claim 75, wherein said linkage analysis
5 or association analysis generates a statistical score for said position in the genome of said species.

77. The computer program product of claim 76, wherein said testing is linkage
analysis and said statistical score is a logarithm of the odds (lod) score.

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78. The computer program product of claim 77, wherein said eQTL is
represented by a lod score that is greater than 2.0.

79. The computer program product of claim 77, wherein said eQTL is
15 represented by a lod score that is greater than 3.0.

80. The computer program product of claim 77, wherein said eQTL is
represented by a lod score that is greater than 4.0.

20 81. The computer program product of claim 77, wherein said eQTL is
represented by a lod score that is greater than 5.0.

82. The computer program product of claim 54, wherein said second QTL
analysis comprises:

25 (i) testing for linkage between (a) the genotype of said plurality of organisms at a
position in the genome of said species and (b) said plurality of phenotypic values;
(ii) advancing the position in said genome by an amount; and
(iii) repeating steps (i) and (ii) until a portion of the genome of said species has
been tested.

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83. The computer program product of claim 82, wherein said amount is less
than 100 centiMorgans.

84. The computer program product of claim 82, wherein said amount is less
35 than 10 centiMorgans.

85. The computer program product of claim 82, wherein said amount is less than 5 centiMorgans.

5 86. The computer program product of claim 82, wherein said amount is less than 2.5 centiMorgans.

87. The computer program product of claim 82, wherein said testing comprises performing linkage analysis or association analysis.

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88. The computer program product of claim 87, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

15 89. The computer program product of claim 88, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

90. The computer program product of claim 89, wherein said cQTL is represented by a lod score that is greater than 2.0.

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91. The computer program product of claim 89, wherein said cQTL is represented by a lod score that is greater than 3.0.

25 92. The computer program product of claim 89, wherein said cQTL is represented by a lod score that is greater than 4.0.

93. The computer program product of claim 89, wherein said cQTL is represented by a lod score that is greater than 5.0.

30 94. The computer program product of claim 54, wherein said plurality of organisms is human.

95. The computer program product of claim 54, wherein said clinical trait T is a complex trait.

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96. The computer program product of claim 95, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

97. The computer program product of claim 95, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.

98. The computer program product of claim 95, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

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99. The computer program product of claim 95, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

100. The computer program product of claim 95, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.

101. The computer program product of claim 95, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

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102. The computer program product of claim 95, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

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103. The computer program product of claim 54, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 40 cM of the physical location of the cQTL in said genome.

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104. The computer program product of claim 54, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 20 cM of the physical location of the cQTL in said genome.

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105. The computer program product of claim 54, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 10 cM of the physical location of the cQTL in said genome.

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106. The computer program product of claim 54, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 6 cM of the physical location of the cQTL in said genome.

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107. A computer system for associating a gene G in the genome of a species with a clinical trait T exhibited by one or more organisms in a plurality of organisms of said species, the computer system comprising:

a central processing unit;

20 a memory, coupled to the central processing unit, the memory storing an expression quantitative trait loci (eQTL) identification module, a clinical quantitative trait loci (cQTL) identification module, and a determination module; wherein

the expression quantitative trait loci (eQTL) identification module comprises instructions for identifying an expression quantitative trait loci (eQTL) for said gene G
25 using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an organism in said plurality of organisms;

the clinical quantitative trait loci (cQTL) identification module comprises
30 instructions for identifying a clinical quantitative trait loci (cQTL) that is linked to said clinical trait T using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for said clinical trait T in an organism in said plurality of organisms; and

the determination module comprises instructions for determining whether said eQTL and said cQTL colocalize to the same locus in the genome of said species, wherein, when said eQTL and said cQTL colocalize to the same locus, said gene G is associated with said clinical trait T.

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108. The computer system of claim 107, wherein said instructions for determining further comprise determining whether the locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species, wherein, when said locus of said eQTL in the genome of said species corresponds to the physical location of said gene G in the genome of said species said gene G is associated with said clinical trait T.

109. The computer system of claim 108, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 3cM of each other in the genome of said species.

110. The computer system of claim 108, wherein said eQTL corresponds to the physical location of said gene G when the eQTL and gene G colocalize within 1cM of each other in the genome of said species.

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111. The computer system of claim 107, wherein said eQTL and said cQTL are not considered colocalized unless a test for pleiotropy indicates that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL.

112. The computer system of claim 107, wherein said first QTL analysis and said second QTL analysis each uses a genetic map that represents the genome of said species.

113. The computer system of claim 112, the memory further storing a genetic map construction module, the genetic map construction module including instructions for constructing said genetic map from a set of genetic markers associated with said plurality of organisms.

114. The computer system of claim 113, wherein said set of genetic markers comprises single nucleotide polymorphisms (SNPs), microsatellite markers, restriction

fragment length polymorphisms, short tandem repeats, DNA methylation markers, sequence length polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

5 115. The computer system of claim 113, wherein genotype data is used by said genetic map construction module, wherein said genotype data comprises knowledge of which alleles, for each marker in said set of genetic markers, are present in each organism in said plurality of organisms.

10 116. The computer system of claim 113, wherein said plurality of organisms represents a segregating population and pedigree data is used in said constructing step, and wherein said pedigree data shows one or more relationships between organisms in said plurality of organisms.

15 117. The computer system of claim 113, wherein said plurality of organisms comprises an F₂ population, a F₁ population, a F_{2:3} population, or a Design III population and said one or more relationships between organisms in said plurality of organisms indicates which organisms in said plurality of organisms are members of said F₂ population, said F₁ population, said F_{2:3} population, or said Design III population.

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 118. The computer system of claim 107, wherein each said expression value is a normalized expression level measurement for said gene G in an organism in said plurality of organisms.

25 119. The computer system of claim 118, wherein each said expression level measurement is determined by measuring an amount of a cellular constituent that corresponds to said gene G in one or more cells from an organism in said plurality of organisms.

30 120. The computer system of claim 119, wherein said amount of said cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, an abundance of a protein in said one or more cells of said organism, an abundance of an mRNA expressing said gene, or a degree of protein modification.

121. The computer system of claim 120, wherein said abundance of said RNA is measured by a method comprising contacting a gene transcript array with said RNA from said one or more cells of said organism, or with nucleic acid derived from said RNA, wherein said gene transcript array comprises a positionally addressable surface with attached nucleic acids or nucleic acid mimics, wherein said nucleic acids or nucleic acid mimics are capable of hybridizing with said RNA species, or with nucleic acid derived from said RNA species.

122. The computer system of claim 121, wherein said normalized expression level measurement is obtained by a normalization technique selected from the group consisting of Z-score of intensity, median intensity, log median intensity, Z-score standard deviation log of intensity, Z-score mean absolute deviation of log intensity, calibration DNA gene set, user normalization gene set, ratio median intensity correction, and intensity background correction.

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123. The computer system of claim 107, wherein said first QTL analysis comprises:

- (i) testing for linkage between (a) the genotype of said plurality of organisms at a position in the genome of said species and (b) said plurality of expression statistics for gene G;
- (ii) advancing the position in said genome by an amount; and
- (iii) repeating steps (i) and (ii) until a portion of the genome of said species has been tested.

124. The computer system of claim 123, wherein said amount is less than 100 centiMorgans.

125. The computer system of claim 123, wherein said amount is less than 10 centiMorgans.

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126. The computer system of claim 123, wherein said amount is less than 5 centiMorgans.

127. The computer system of claim 123, wherein said amount is less than 2.5 centiMorgans.

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128. The computer system of claim 123, wherein said testing comprises performing linkage analysis or association analysis.

5 129. The computer system of claim 128, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

10 130. The computer system of claim 129, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

131. The computer system of claim 130, wherein said eQTL is represented by a lod score that is greater than 2.0.

15 132. The computer system of claim 130, wherein said eQTL is represented by a lod score that is greater than 3.0.

133. The computer system of claim 130, wherein said eQTL is represented by a lod score that is greater than 4.0.

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134. The computer system of claim 130, wherein said eQTL is represented by a lod score that is greater than 5.0.

25 135. The computer system of claim 107, wherein said second QTL analysis comprises:

(i) testing for linkage between (a) the genotype of said plurality of organisms at a position in the genome of said species and (b) said plurality of phenotypic values;

(ii) advancing the position in said genome by an amount; and

30 (iii) repeating steps (i) and (ii) until a portion of the genome of said species has been tested.

136. The computer system of claim 135, wherein said amount is less than 100 centiMorgans.

137. The computer system of claim 135, wherein said amount is less than 10 centiMorgans.

138. The computer system of claim 135, wherein said amount is less than 5 centiMorgans.

139. The computer system of claim 135, wherein said amount is less than 2.5 centiMorgans.

140. The computer system of claim 135, wherein said testing comprises performing linkage analysis or association analysis.

141. The computer system of claim 140, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

142. The computer system of claim 141, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

143. The computer system of claim 142, wherein said cQTL is represented by a lod score that is greater than 2.0.

144. The computer system of claim 142, wherein said cQTL is represented by a lod score that is greater than 3.0.

145. The computer system of claim 142, wherein said cQTL is represented by a lod score that is greater than 4.0.

146. The computer system of claim 142, wherein said cQTL is represented by a lod score that is greater than 5.0.

147. The computer system of claim 107, wherein said plurality of organisms is human.

148. The computer system of claim 107, wherein said clinical trait T is a complex trait.

149. The computer system of claim 148, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

150. The computer system of claim 148, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.

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151. The computer system of claim 148, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

152. The computer system of claim 148, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

153. The computer system of claim 148, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.

154. The computer system of claim 148, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

155. The computer system of claim 148, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

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156. The computer system of claim 107, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 40 cM of the physical location of the cQTL in said genome.

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157. The computer system of claim 107, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 20 cM of the physical location of the cQTL in said genome.

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158. The computer system of claim 107, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 10 cM of the physical location of the cQTL in said genome.

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159. The computer system of claim 107, wherein said eQTL and said cQTL colocalize to the same locus in the genome of said species when the physical location of the eQTL in said genome is within 6 cM of the physical location of the cQTL in said genome.

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160. A method for determining the topology of a biological pathway that affects a complex trait, the method comprising:

(A) identifying one or more expression quantitative trait loci (eQTL) for a gene in a plurality of genes using a first quantitative trait loci (QTL) analysis, wherein said first
20 QTL analysis uses a plurality of expression statistics for the gene as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for the gene in an organism in a plurality of organisms of a species;

(B) repeating step (A) a first number of times, wherein each repetition of step (A) uses a different gene in said plurality of genes;

25 (C) identifying a clinical quantitative trait loci (cQTL) that is linked to a clinical trait in a plurality of clinical traits using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values is a phenotypic value for the clinical trait in the plurality of clinical traits in an organism in said plurality of organisms;

30 (D) repeating step (C) a second number of times, wherein each repetition of step (C) uses a different clinical trait in a plurality of clinical traits; and

(E) using (i) an identity of each eQTL, identified in an iteration of step (A), that colocalizes with a cQTL, identified in an iteration of step (C), and (ii) a physical location of each gene in said plurality of genes on a molecular map for said species, in order to
35 determine the topology of said biological pathway that affects said complex trait.

161. The method of claim 160, wherein three or more clinical traits are analyzed in respective iterations of step (C).

5 162. The method of claim 160, wherein eight or more clinical traits are analyzed in respective iterations of step (C).

163. The method of claim 160, wherein three or more genes are analyzed in respective iterations of step (A).

10

164. The method of claim 160, wherein eight or more genes are analyzed in respective iterations of step (A).

165. The method of claim 160, wherein said molecular map is a marker map
15 and an eQTL is colocalized with a cQTL when the eQTL and the cQTL fall within 1 cM of each other on said marker map.

166. The method of claim 160, wherein said molecular map is a genomic map
and an eQTL is colocalized with a cQTL when they fall within 500 bases of each other on
20 said genomic map.

167. The method of claim 160, wherein said first QTL analysis and said second QTL analysis each uses a genetic map that represents the genome of said species.

25 168. The method of claim 160, wherein said genetic map is constructed from single nucleotide polymorphisms (SNPs), microsatellite markers, restriction fragment length polymorphisms, short tandem repeats, DNA methylation markers, sequence length polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

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169. The method of claim 160, wherein each said expression value is a normalized expression level measurement for the gene in an organism in said plurality of organisms.

170. The method of claim 169, wherein each said expression level measurement is determined by measuring an amount of a cellular constituent that corresponds to the gene in one or more cells from an organism in said plurality of organisms.

5 171. The method of claim 170, wherein said amount of said cellular constituent comprises an abundance of an RNA present in said one or more cells of said organism, an abundance of a protein in said one or more cells of said organism, an abundance of an mRNA expressing said gene, or a degree of protein modification.

10 172. The method of claim 170, wherein said abundance of said RNA is measured by a method comprising contacting a gene transcript array with said RNA from said one or more cells of said organism, or with nucleic acid derived from said RNA, wherein said gene transcript array comprises a positionally addressable surface with
15 attached nucleic acids or nucleic acid mimics, wherein said nucleic acids or nucleic acid mimics are capable of hybridizing with said RNA species, or with nucleic acid derived from said RNA species.

 173. The method of claim 169, wherein said normalized expression level measurement is obtained by a normalization technique selected from the group consisting
20 of Z-score of intensity, median intensity, log median intensity, Z-score standard deviation log of intensity, Z-score mean absolute deviation of log intensity, calibration DNA gene set, user normalization gene set, ratio median intensity correction, and intensity background correction.

25 174. The method of claim 160, wherein said first QTL analysis comprises:
 (i) testing for linkage between (a) a genotype of said plurality of organisms at a position in a genome of said species and (b) said plurality of expression statistics for the gene;
 (ii) advancing the position in said genome by an amount; and
30 (iii) repeating steps (i) and (ii) until a portion of the genome of said species has been tested.

 175. The method of claim 174, wherein said testing comprises performing linkage analysis or association analysis.

176. The method of claim 175, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

177. The method of claim 176, wherein said testing is linkage analysis and said
5 statistical score is a logarithm of the odds (lod) score.

178. The method of claim 177, wherein said eQTL is represented by a lod score that is greater than 3.0.

10 179. The method of claim 160, wherein said second QTL analysis comprises:
(i) testing for linkage between (a) the genotype of said plurality of organisms at a position in a genome of said species and (b) said plurality of phenotypic values;
(ii) advancing the position in said genome by an amount; and
(iii) repeating steps (i) and (ii) until a portion the genome of said species has been
15 tested.

180. The method of claim 179, wherein said testing comprises performing linkage analysis or association analysis.

20 181. The method of claim 180, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

182. The method of claim 181, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

25 183. The method of claim 182, wherein said cQTL is represented by a lod score that is greater than 3.0.

184. The method of claim 160, wherein said species is human.
30

185. The method of claim 160, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

186. The method of claim 160, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.

5 187. The method of claim 160, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

188. The method of claim 160, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

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189. The method of claim 160, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.

190. The method of claim 160, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

191. The method of claim 160, wherein said complex trait is asthma, ataxia, telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

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192. A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism for determining the topology of a biological pathway that affects a complex trait, the computer program mechanism comprising:

30 an expression quantitative trait loci (eQTL) identification module, the eQTL identification module comprising:

instructions for identifying one or more expression quantitative trait loci (eQTL) for a gene in a plurality of genes using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for the gene as a

35

quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for the gene in an organism in a plurality of organisms of a species; and

instructions for repeating a first number of times said instructions for identifying
5 one or more eQTL for a gene, wherein each repetition of said instructions for identifying one or more eQTL for a gene uses a different gene in said plurality of genes;

a clinical quantitative trait loci (cQTL) identification module; the cQTL identification module comprising:

instructions for identifying a clinical quantitative trait loci (cQTL) that is linked to
10 a clinical trait in a plurality of clinical traits using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for the clinical trait in the plurality of clinical traits in an organism in said plurality of organisms; and

15 instructions for repeating a second number of times said instructions for identifying one or more cQTL that is linked to a clinical trait, wherein each repetition of said instructions for identifying one or more cQTL that is linked to a clinical trait uses a different clinical trait in a plurality of clinical traits; and

a determination module, said determination module comprising:

20 instructions for using (i) the identity of each eQTL, identified by said eQTL identification module, that colocalizes with a cQTL, identified by said cQTL identification module, and (ii) a physical location of each gene in said plurality of genes in a molecular map for said species, in order to determine the topology of a biological pathway that affects a complex trait.

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193. The computer program product of claim 192, wherein three or more clinical traits are analyzed by said cQTL identification module.

194. The computer program product of claim 192, wherein eight or more
30 clinical traits are analyzed by said cQTL identification module.

195. The computer program product of claim 192, wherein three or more genes are analyzed by said eQTL identification module.

196. The computer program product of claim 192, wherein eight or more genes are analyzed by said eQTL identification module.

197. The computer program product of claim 192, wherein said molecular map
5 is a marker map and an eQTL is colocalized with a cQTL when the eQTL and the cQTL fall within 1 cM of each other on said marker map.

198. The computer program product of claim 192, wherein said molecular map
10 is a genomic map and an eQTL is colocalized with a cQTL when they fall within 500 bases of each other on said genomic map.

199. The computer program product of claim 192, wherein said first QTL
analysis and said second QTL analysis each uses a marker map that represents the
genome of said species.
15

200. The computer program product of claim 199, wherein said marker map is
constructed from single nucleotide polymorphisms (SNPs), microsatellite markers,
restriction fragment length polymorphisms, short tandem repeats, DNA methylation
markers, sequence length polymorphisms, random amplified polymorphic DNA,
20 amplified fragment length polymorphisms, or simple sequence repeats.

201. The computer program product of claim 192, wherein each said expression
value is a normalized expression level measurement for the gene in an organism in said
plurality of organisms.
25

202. The computer program product of claim 192, wherein said first QTL
analysis comprises:

- (i) instructions for testing for linkage between (a) a genotype of said plurality of
organisms at a position in a genome of said species and (b) said plurality of expression
30 statistics for the gene;
- (ii) instructions for advancing the position in said genome by an amount; and
- (iii) instructions for repeating instructions (i) and instructions (ii) until a portion of
the genome of said species has been tested.

203. The computer program product of claim 202, wherein said testing comprises performing linkage analysis or association analysis.

204. The computer program product of claim 203, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

205. The computer program product of claim 204, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

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206. The computer program product of claim 205, wherein said eQTL is represented by a lod score that is greater than 3.0.

207. The computer program product of claim 192 wherein said second QTL analysis comprises:

15

(i) instructions for testing for linkage between (a) the genotype of said plurality of organisms at a position in a genome of said species and (b) said plurality of phenotypic values;

(ii) instructions for advancing the position in said genome by an amount; and

20

(iii) instructions for repeating instructions (i) and instructions (ii) until a portion the genome of said species has been tested.

208. The computer program product of claim 207, wherein said testing comprises performing linkage analysis or association analysis.

25

209. The computer program product of claim 208, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

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210. The computer program product of claim 209, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

211. The computer program product of claim 210, wherein said cQTL is represented by a lod score that is greater than 3.0.

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212. The computer program product of claim 192, wherein said species is human.

213. The computer program product of claim 192, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

214. The computer program product of claim 192, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits no predisposing allele to said disease.

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215. The computer program product of claim 192, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

216. The computer program product of claim 192, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

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217. The computer program product of claim 192, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.

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218. The computer program product of claim 192, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

219. The computer program product of claim 192, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

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220. A computer system for determining the topology of a biological pathway that affects a complex trait, the computer system comprising:

35 a central processing unit;

a memory, coupled to the central processing unit, the memory storing an expression quantitative trait loci (eQTL) identification module, a clinical quantitative trait loci (cQTL) identification module, and a determination module; wherein

the eQTL identification module comprises:

5 instructions for identifying one or more expression quantitative trait loci (eQTL) for a gene in a plurality of genes using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for the gene as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for the gene in an organism in a plurality of organisms of a
10 species; and

instructions for repeating a first number of times said instructions for identifying one or more eQTL for a gene, wherein each repetition of said instructions for identifying one or more eQTL for a gene uses a different gene in said plurality of genes;

the cQTL identification module comprises:

15 instructions for identifying a clinical quantitative trait loci (cQTL) that is linked to a clinical trait in a plurality of clinical traits using a second QTL analysis, wherein said second QTL analysis uses a plurality of phenotypic values as a quantitative trait, wherein each phenotypic value in said plurality of phenotypic values represents a phenotypic value for the clinical trait in the plurality of clinical traits in an organism in said plurality of
20 organisms; and

instructions for repeating a second number of times said instructions for identifying one or more cQTL that is linked to a clinical trait, wherein each repetition of said instructions for identifying one or more cQTL that is linked to a clinical trait uses a different clinical trait in a plurality of clinical traits; and

25 the determination module comprises:

instructions for using (i) the identity of each eQTL, identified by said eQTL identification module, that colocalizes with a cQTL, identified by said cQTL identification module, and (ii) a physical location of each gene in said plurality of genes in a molecular map for said species, in order to determine the topology of a biological
30 pathway that affects a complex trait.

221. The computer system of claim 220, wherein three or more clinical traits are analyzed by said cQTL identification module.

222. The computer system of claim 220, wherein eight or more clinical traits are analyzed by said cQTL identification module.

223. The computer system of claim 220, wherein three or more genes are
5 analyzed by said eQTL identification module.

224. The computer system of claim 220, wherein eight or more genes are analyzed by said eQTL identification module.

10 225. The computer system of claim 220, wherein said molecular map is a marker map and an eQTL is colocalized with a cQTL when the eQTL and the cQTL fall within 1 cM of each other on said marker map.

226. The computer system of claim 220, wherein said molecular map is a
15 genomic map and an eQTL is colocalized with a cQTL when they fall within 500 bases of each other on said genomic map.

227. The computer system of claim 220, wherein said first QTL analysis and said second QTL analysis each uses a marker map that represents the genome of said
20 species.

228. The computer system of claim 227, wherein said marker map is constructed from single nucleotide polymorphisms (SNPs), microsatellite markers, restriction fragment length polymorphisms, short tandem repeats, DNA methylation
25 markers, sequence length polymorphisms, random amplified polymorphic DNA, amplified fragment length polymorphisms, or simple sequence repeats.

229. The computer program system of claim 220, wherein each said expression value is a normalized expression level measurement for the gene in an organism in said
30 plurality of organisms.

230. The computer system of claim 220, wherein said first QTL analysis comprises:

(i) instructions for testing for linkage between (a) a genotype of said plurality of organisms at a position in a genome of said species and (b) said plurality of expression statistics for the gene;

(ii) instructions for advancing the position in said genome by an amount; and

5 (iii) instructions for repeating instructions (i) and instructions (ii) until a portion of the genome of said species has been tested.

231. The computer system of claim 230, wherein said testing comprises performing linkage analysis or association analysis.

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232. The computer system of claim 231, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

15

233. The computer system of claim 232, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

234. The computer system of claim 233, wherein said eQTL is represented by a lod score that is greater than 3.0.

20

235. The computer system of claim 220, wherein said second QTL analysis comprises:

(i) instructions for testing for linkage between (a) the genotype of said plurality of organisms at a position in a genome of said species and (b) said plurality of phenotypic values;

25

(ii) instructions for advancing the position in said genome by an amount; and

(iii) instructions for repeating instructions (i) and instructions (ii) until a portion the genome of said species has been tested.

30

236. The computer system of claim 235, wherein said testing comprises performing linkage analysis or association analysis.

237. The computer system of claim 236, wherein said linkage analysis or association analysis generates a statistical score for said position in the genome of said species.

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238. The computer system of claim 237, wherein said testing is linkage analysis and said statistical score is a logarithm of the odds (lod) score.

5 239. The computer system of claim 238, wherein said cQTL is represented by a lod score that is greater than 3.0.

240. The computer system of claim 220, wherein said species is human.

10 241. The computer system of claim 220, wherein said complex trait is characterized by an allele that exhibits incomplete penetrance in said species.

242. The computer system of claim 220, wherein said complex trait is a disease that is contracted by an organism in said population, and wherein said organism inherits
15 no predisposing allele to said disease.

243. The computer system of claim 220, wherein said complex trait arises when any of a plurality of different genes in the genome of said species is mutated.

20 244. The computer system of claim 220, wherein said complex trait requires the simultaneous presence of mutations in a plurality of genes in the genome of said species.

245. The computer system of claim 220, wherein said complex trait is associated with a high frequency of disease-causing alleles in said species.
25

246. The computer system of claim 220, wherein said complex trait is a phenotype that does not exhibit Mendelian recessive or dominant inheritance attributable to a single gene locus.

30 247. The computer system of claim 220, wherein said complex trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-

dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

248. The method of claim 1, the method further comprising:

5 determining whether said eQTL for said gene G appears in a third quantitative trait loci analysis, wherein said third QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an organism in said plurality of organisms in which said gene has been knocked out.

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249. The method of claim 248 wherein said gene is knocked out using *in vivo* siRNA, a gene knock-out mouse strain, or a transgenic mouse strain.

250. The computer program product of claim 54, the computer program
15 mechanism further comprising:

a validation module for determining whether said eQTL for said gene G appears in a third quantitative trait loci analysis, wherein said third QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an
20 organism in said plurality of organisms in which said gene has been knocked out.

251. The computer system of claim 107, the memory further comprising:

a validation module that comprises instructions for determining whether said eQTL for said gene G appears in a third quantitative trait loci analysis, wherein said third
25 QTL analysis uses a plurality of expression statistics for gene G as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for gene G in an organism in said plurality of organisms in which said gene has been knocked out.

30 252. The method of claim 1, the method further comprising:

(D) validating said association between said gene G and said clinical trait T by testing for genetic linkage between said expression quantitative trait loci (eQTL) and said clinical quantitative trait loci (cQTL).

253. The method of claim 252 wherein said testing for genetic linkage comprises marker-difference regression or a multiple-trait extension of composite interval mapping.

254. The computer program product of claim 54, the computer program
5 mechanism further comprising instructions for validating said association between said gene G and said clinical trait T by testing for genetic linkage between said expression quantitative trait loci (eQTL) and said clinical quantitative trait loci (cQTL).

255. The computer program product of claim 254 wherein said testing for genetic
10 linkage comprises marker-difference regression or a multiple-trait extension of composite interval mapping.

256. The computer system of claim 107, the computer the memory further
comprising instructions for validating said association between said gene G and said
15 clinical trait T by testing for genetic linkage between said expression quantitative trait loci (eQTL) and said clinical quantitative trait loci (cQTL).

257. The computer system of claim 256 wherein said testing for genetic linkage
comprises marker-difference regression or a multiple-trait extension of composite interval
20 mapping.

258. The method of claim 5 wherein said test for pleiotropy comprises comparing
a null hypothesis, indicating that said eQTL and said cQTL are represented by a QTL that
is common to both said eQTL and said cQTL, to an alternative hypothesis, indicating
25 linkage disequilibrium.

259. The method of claim 258 wherein said null hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} Q + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

30 wherein

Q is a categorical random variable indicating the genotypes at the position of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and μ_i and β_i are model parameters.

5 260. The method of claim 258 wherein the alternative hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

10 $\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and

μ_i and β_i are model parameters.

261. The method of claim 258 wherein the alternative hypothesis is:

15
$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

20 covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$;

μ_i and β_i are model parameters; and

one of conditions (i) through (iv) is valid:

(i) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 = 0$;

(ii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 = 0$;

25 (iii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 \neq 0$; and

(iv) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 \neq 0$.

262. The method of claim 258 wherein the negative loglikelihood for the null hypothesis and the alternative hypothesis are minimized using maximum likelihood analysis thereby forming a likelihood ratio test statistic.

263. The computer program product of claim 58 wherein said test for pleiotropy comprises comparing a null hypothesis, indicating that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL, to an alternative hypothesis, indicating linkage disequilibrium.

264. The computer program product of claim 263 wherein said null hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} Q + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

15 wherein

Q is a categorical random variable indicating the genotypes at the position of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and

20 μ_i and β_i are model parameters.

265. The computer program product of claim 263 wherein the alternative hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

25 wherein

Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and

μ_i and β_i are model parameters.

- 5 266. The computer program product of claim 263 wherein the alternative hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

- 10 Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$;

μ_i and β_i are model parameters; and

one of conditions (i) through (iv) is valid:

- 15 (i) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 = 0$;
 (ii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 = 0$;
 (iii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 \neq 0$; and
 (iv) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 \neq 0$.

- 20 267. The computer program product of claim 263 wherein the negative loglikelihood for the null hypothesis and the alternative hypothesis are minimized using maximum likelihood analysis thereby forming a likelihood ratio test statistic.

- 25 268. The computer system of claim 111 wherein said test for pleiotropy comprises comparing a null hypothesis, indicating that said eQTL and said cQTL are represented by a QTL that is common to both said eQTL and said cQTL, to an alternative hypothesis, indicating linkage disequilibrium.

269. The computer program product of claim 268 wherein said null hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix} Q + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

- 5 Q is a categorical random variable indicating the genotypes at the position of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and

μ_i and β_i are model parameters.

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270. The computer program product of claim 268 wherein the alternative hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

- 15 Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and

covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$; and

μ_i and β_i are model parameters.

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271. The computer program product of claim 268 wherein the alternative hypothesis is:

$$\begin{pmatrix} y_1 \\ y_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \beta_1 & \beta_2 \\ \beta_3 & \beta_4 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix},$$

wherein

- 25 Q_1 and Q_2 are categorical random variables indicating the genotypes at the positions of said eQTL and said cQTL in said plurality of organisms;

$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$ is distributed as a bivariate normal random variable with mean $\begin{pmatrix} 0 \\ 0 \end{pmatrix}$ and covariance matrix $\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix}$;

μ_i and β_i are model parameters; and
one of conditions (i) through (iv) is valid:

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- (i) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 = 0$;
- (ii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 = 0$;
- (iii) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 = 0$, and $\beta_3 \neq 0$; and
- (iv) $\beta_1 \neq 0$, $\beta_4 \neq 0$, $\beta_2 \neq 0$, and $\beta_3 \neq 0$.

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272. The computer program product of claim 268 wherein the negative loglikelihood for the null hypothesis and the alternative hypothesis are minimized using maximum likelihood analysis thereby forming a likelihood ratio test statistic.